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REVIEW

Hyper-IgD syndrome/mevalonate kinase deficiency: what is new?

C. M. Mulders-Manders[1] · **A. Simon**[1]

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Abstract Mevalonate kinase deficiency or hyper-IgD syndrome is a hereditary autoinflammatory syndrome caused by mutations in the mevalonate kinase gene. In this review, we will discuss new findings in this disorder that have been published in the last 2 years. This includes new insights into pathophysiology, treatment, and the clinical phenotype linked to the genetic defect.

Introduction

The hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is an autoinflammatory disease characterized by recurrent episodes of fever, cervical lymphadenopathy, hepatomegaly, splenomegaly, abdominal pain, skin rash, arthralgia, and other inflammatory symptoms [1] accompanied by increased inflammatory markers such as C-reactive protein (CRP) and serum amyloid A (SAA). Febrile attacks can be triggered by childhood vaccinations or minor infection, although the triggers for most attacks are unknown. The name HIDS was derived from the fact that in the first case series, increased serum levels of immunoglobulin D (IgD) were found in all patients with this syndrome. Now that the genetic background is known, the currently more accurate name for the disorder is mevalonate kinase deficiency (MKD).

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✉ A. Simon
Anna.Simon@radboudumc.nl

[1] Department of Internal Medicine, Nijmegen Centre for Immunodeficiency and Autoinflammation (NCIA), Radboud University Medical Center, Nijmegen, The Netherlands

MKD is caused by loss of function mutations in the mevalonate kinase gene (MVK) [2], which encodes for the protein mevalonate kinase. Mevalonate kinase is the second enzyme in the common pathway leading to both cholesterol and non-sterol isoprenoids and is located directly downstreams of HMG-CoA-reductase. Mevalonate kinase catalyses the phosphorylation of mevalonic acid to 5-phosphomevalonate (Fig. 1). Non-sterol isoprenoid end products are involved in the prenylation of proteins, where either a farnesyl group or a geranylgeranyl group is attached to a protein. This process is necessary for adequate protein function. Deficiency of mevalonate kinase leads to a shortage of intermediate compounds and end products of this pathway.

The level of remaining mevalonate kinase enzyme activity in MKD determines the clinical phenotype. Apart from the abovementioned clinical phenotype of HIDS, MKD can also present as mevalonate aciduria, a severe disease characterized by neurologic involvement with psychomotor retardation, cerebellar ataxia, and facial dysmorphy besides the inflammatory symptoms, leading to early death. MKD forms a continuous spectrum of disease between these two clinical entities. Overlapping clinical syndromes are seen with increasing frequency. As there is no clear border between phenotypes, we will use the term *mevalonate kinase deficiency*, which encompasses both HIDS and mevalonate aciduria, to describe the disease in this paper.

In this review, we will discuss new findings in MKD that have been published between January 1, 2012 and December 31, 2014.

What is new on the pathophysiological mechanism of MKD?

In the past 30 years, MKD has been proven to be a typical monogenetic autoinflammatory disease with overproduction

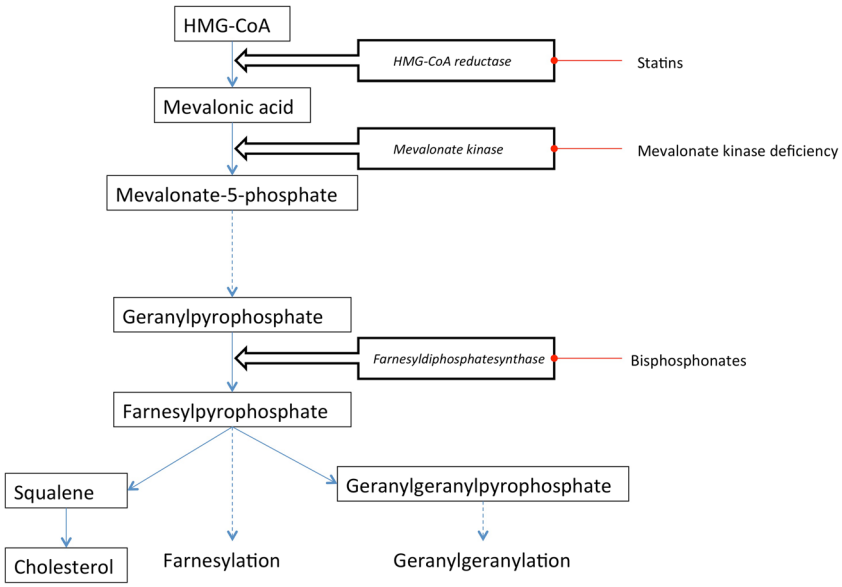

Fig. 1 Mevalonate kinase catalyses the phosphorylation of mevalonic acid to 5-phosphomevalonate

of the inflammatory cytokine interleukin-1 beta (IL-1β) as prominent pathophysiological mechanism [3–7]. The importance of this cytokine in MKD is backed up by the beneficial effects of IL-1β-targeting drugs such as anakinra in patients with this disease [8–11].

Most studies on the pathophysiology of MKD are based on in vitro cellular models with murine [12–14] or human cells with drug-induced block of the mevalonate kinase pathway with either HMG-CoA reductase inhibitors or bisphosphonates (Fig. 1). In these models, LPS or other bacterial components are used to mimic the inflammatory stimulus needed for the production of IL-1β. Stimulation of monocytes with LPS leads to increased pro-IL-1β transcription via activation of transcription factor NF-kB [5]. The effects of bisphosphonates on inflammation in mice were proven not to be strain-specific [15]. Besides cellular in vitro models, two in vivo animal models for MKD have been proposed. The first model uses heterozygote MVK knockdown mice that show a MKD-like phenotype with elevated body temperature, hepatosplenomegaly, and increased serum IgD [16]. With the use of this model, altered expression of stimulatory and inhibitory B7 glycoproteins on lymphocytes and macrophages with possible altered balance between stimulatory and inhibitory signals, as well as differences in cell proliferation between wild-type and knockdown mice, has been found. Interestingly, in these experiments, a difference between male and female mice was seen [17], although in humans, no gender-specific difference in clinical phenotype has been described.

In a second animal model of MKD, Balb/c mice are intraperitoneally injected with bisphosphonates 2 or 3 days prior to inflammatory stimulation followed by decapitation and analysis of inflammatory markers such as cytokines, peritoneal exudates, or splenic infiltration [15, 18, 19]. Comparison of the cytokine profile of these mice with the cytokine profile of healthy controls and MKD patients showed few discrepancies between the murine model and human monocytes, with increased IL-6 expression only in MKD patients and mouse-specific increased anti-TNF-α expression [20]. Extrapolation of the results from murine models to humans can be questioned as it has been proven that bisphosphonates might actually be able to be beneficial in MKD: A single patient with MKD treated with weekly bisphosphonates because of secondary osteoporosis showed complete resolution of the febrile episodes, which returned when the drug was ceased and disappeared again at reintroduction [21]. Thus, the pro-inflammatory effect of bisphosphonates may differ between species or between in vitro/in vivo experimental settings.

The link between increased IL-1β secretion and mevalonate kinase deficiency in MKD is most likely mediated by defective protein prenylation. In prenylation, non-sterol isoprenoids, such as farnesyl pyrophosphate (FPP) or geranylgeranyl pyrophosphate (GGPP) are coupled to a target protein, affecting its activity or cellular location. In a human monocytic MKD model, deficiency of GGPP leads to overproduction of IL-1β [22, 6, 23]. The deficiency of GGPP was shown to lead to defective prenylation of RhoA, rendering this protein inactive. Inactivity of RhoA results in increased activity of Rac1 and consequent activation of PKB [24]. Other small GTPases may also be affected. The Rac1/PI3K/PKB pathway had been linked to the pathogenesis of MKD earlier [5]. Liao et al. reported Rac1-independent increased IL-1β secretion in MKD [23]. Inactivation of RhoA was able to induce IL-1β mRNA transcription independent of NLRP3- or caspase-1 activity [24]. The B7 glycoproteins that were found to be affected in the earlier described murine MKD model are also prenylation-dependent [17].

Recently, several papers have focused on disrupted mitochondrial function in the pathophysiology of MKD. Possible

involvement of mitochondria was suggested by the observation that in a murine cell model, inhibition of the mevalonate kinase pathway by HMG-CoA reductase inhibitors led to increased programmed cell death via caspase-3 and caspase-9, the latter being activated via an intrinsic mitochondrial pathway [25]. Mevalonate kinase deficiency leads to formation of elongated, instable mitochondria due to defective RhoA prenylation [14, 26, 24]. The aberrant mitochondria would normally be cleared from the cytosol by autophagia, but in MKD, clearance of the defective mitochondria is disrupted. Because of this defect, mitochondrial DNA accumulates in the cytosol and is able to bind and activate NLRP3, inducing IL-1β secretion [26]. Reactive oxygen species, but not specifically mitochondrial reactive oxygen species (mROS), are involved in this [26, 14]. Thus, both NLRP3-dependent as well as NLRP3-independent routes of IL-1β activation may be involved in the pathogenesis of MKD [26, 24].

IL-1β is not the only cytokine involved in the inflammatory response in MKD. PBMCs of MKD patients show a significantly different pattern of pro-inflammatory cytokine secretion after specific stimulation of several toll-like receptors (TLRs), including TLR4, TLR2, and nucleotide oligomerization domain-containing 2 (NOD2). Apart from IL-1β, there was increased expression of IL-1α, TNF, and IL-6 compared to PBMCs of healthy controls. Incubation of PBMCs from MKD patients with anakinra led to a normalization of cytokine expression (including TNF and IL-6) [11]. Marcuzzi et al. also observed increased expression of several different proinflammatory cytokines in their murine model [20]. These findings fit with the clinical observation that anti-IL-1β-treatment in MKD is not fully effective in all patients [11].

A probable explanation for the neurologic symptoms of severe MKD was suggested by Marcuzzi et al. In a neuroblastoma cell line, lovastatin was used as inhibitor of the mevalonate kinase pathway. Incubation of neuroblastoma cells with lovastatin led to a significant increase in programmed cell death with increased caspase-3 and caspase-9 activity, and this was inhibited by the addition of the isoprenoid end product GGOH [25]. Also, in mice, bisphosphonate treatment leads to microglial activation and intracerebral NLRP3 expression [15].

The enzyme deficiency in MKD results in an increased concentration of mevalonic acid, the substrate for mevalonate kinase, in plasma and urine. In mildly affected patients, this increase can be subtle, and accurate measurement can be tricky. Rodrigues et al. developed and validated an improved LC-MS/MS-based quantification assay for mevalonic acid which was tested in human as well as in rat samples [48].

What is new on the treatment of mevalonate kinase deficiency?

The beneficial role of IL-1 targeting drugs as a therapy for MKD has been clear since the introduction of the IL-1 receptor antagonist anakinra. Anakinra binds the IL-1 receptor, preventing the actions of both IL-1α and IL-1β, and it has been shown to reduce the clinical and biochemical inflammation in MKD. It effectively decreases the frequency and severity of inflammatory attacks when used on a daily basis [8–10]. In patients with infrequent attacks, on-demand treatment (i.e., anakinra is started at the first signs of an inflammatory attack and ceased again after a few days) has been shown to be effective [8]. The major disadvantage of anakinra is the occurrence of painful injection site reactions. A single case report described clinical deterioration instead of improvement in a 12-year-old MKD patient when anakinra was initiated 2 days into a febrile attack with resolution of symptoms and inflammatory markers when anakinra was stopped again 5 days after it was started [27]. A possible concomitant infection aggravated by the IL-1-receptor blockage might explain these findings.

Canakinumab, a long acting monoclonal antibody directed against IL-1β has shown to be effective in reducing both frequency and severity in patients with mild and severe MKD in case reports and observational case series. Galeotti et al. describe six patients with MKD who were treated with canakinumab 2–7 mg/kg every 4 to 8 weeks. Three patients showed partial response with decreased frequency and severity of the inflammatory attacks. The other half had complete response, defined as no fever attacks and no inflammatory syndrome, during 10 to 21 months of treatment [28], and canakinumab was more effective than anakinra with regard to inhibiting the inflammatory response with fewer side effects in these patients [28]. Another patient who received canakinumab 4 mg/kg every 4 weeks as primary treatment for suspected MKD showed complete clinical response during 12 months of treatment, although biochemical inflammatory parameters remained elevated all this time [29]. In the Eurofever registry, a large international retrospective database on autoinflammatory diseases including 67 patients with MKD, complete response (no disease signs or symptoms and normalization of inflammatory markers) on canakinumab was seen in one of two patients, while the other one responded partially [10].

Most MKD patients benefit from anti-IL-1 therapy. However, anti-IL-1-resistant disease may occur. In a small number of case reports of patients unresponsive to anakinra, the effect of tocilizumab, a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor, has been detailed. Shendi et al. treated a young woman in whom anakinra was ineffective with tocilizumab 8 mg/kg every 4 weeks (the standard dose scheme in rheumatoid arthritis) and found effective reduction of clinical and biochemical inflammation [30]. Two additional MKD patients treated with tocilizumab are described by Stoffels et al., who also observed reduction of frequency and severity of the inflammatory attacks, although after several months of treatment one of these two patients persistently showed mild inflammatory symptoms in the absence of biochemical inflammatory markers [11].

Anti-TNF therapy might be effective in MKD, but the effect is mostly partial and therapy failure and clinical deterioration have been described frequently in patients on infliximab or etanercept [10]. A beneficial effect of human monoclonal anti-TNFα antibody adalimumab was seen in a small number of MKD patients, where the two patients in the Eurofever registry that were treated with adalimumab showed only partial or no response [10, 31].

Several case reports, including one in the past 2 years, describe a beneficial effect of hematopoietic stem cell transplantation on the neurologic and inflammatory symptoms in severe mevalonate kinase deficiency [32–34]. Improvement of cerebral myelinisation on MRI after allogenic stem cell transplantation was seen in one girl [32]. This patient also showed resolution of spastic diplegia following liver transplantion, although this finding might be influenced by the start of physiotherapy directly after the transplantation. Liver transplantation did not influence febrile attacks in this patient [32]. These results could indicate that stem cell transplantation offers a curative option for severe MKD, especially for its neurological features.

Extending the spectrum of mevalonate kinase deficiency

As previously described, MKD forms a spectrum of disease and can therefore present with a diversity of symptoms. In the past 2 years, it became clear that three more or less seemingly unrelated clinical presentations are associated with mutations in MVK (Table 1).

A new initial presentation of MKD was described in two patients with neonatal onset severe ulcerative colitis. In these patients, compound heterozygous mutations in MVK and increased urinary mevalonic acid excretion were found. Both patients presented with bloody diarrhea and abdominal pain. One of these patients also suffered from early onset fever; in the other, the first febrile episode occurred several months after the initial abdominal symptoms. Treatment with anakinra resulted in clinical and biochemical improvement in these patients [35]. A genome-wide association study in six children with mild to severe early onset colitis and a proven MVK mutation showed variants that have previously been linked to IBD in all of them [36], illustrating a possible genetic relation between MKD and IBD. IBD-like symptoms can indeed be part of the clinical phenotype of the HIDS-type of MKD as well.

Other rare or new presentations of MKD that were recently reported are cyclic neutropenia between febrile attacks in a young Israelian boy with homozygous V337I mutation [37], hepatitis [32, 38, 39], and macrophage activation syndrome in an American girl with compound heterozygous MVK mutations and a perforin polymorphism [38].

Retinitis pigmentosa is a clinical syndrome characterized by night blindness and peripheral vision loss. Retinitis pigmentosa has been described previously as a rare and severe complication of MKD. In a large cohort of retinitis pigmentosa patients lacking a genetic defect, three patients harboring homozygous mutations in MVK were found. These three patients seemed to have isolated retinitis pigmentosa, without a clinical phenotype of MKD otherwise, although two of these patients reported recurrent febrile episodes during childhood and had current mild symptoms that could be MKD related. The third patient did not have any signs of MKD. However, this patient was using a HMG-CoA reductase inhibitor because of ischemic heart disease, which may have influenced the phenotype. Severely decreased serum mevalonate kinase activity, and increased urinary mevalonic acid excretion was found in all three patients. Two out of three showed increased serum IgD concentrations [40].

Disseminated superficial actinic porokeratosis (DSAP) is an autosomal dominant hereditary skin disease characterized by annular keratotic lesion predominantly located on sun-exposed parts of the skin. Heterozygous mutations in MVK were identified by exome sequencing in several familial and sporadic DSAP cases [41–43]. Several more case reports have since appeared [44–46], all of them from patients of Asiatic origin. Although some of the mutations identified have also been found in MKD, most mutations were splice site mutations, the studied DSAP patients did not show any clinical signs of MKD, and porokeratosis is not a known feature of MKD [41, 44]. In DSAP, no abnormal IgD serum levels have been described [41]. The effect of the MVK mutations associated with DSAP on enzyme activity has not been studied to date. In a Chinese family with porokeratosis of Mibelli, a dermatological disease closely related to DSAP, a novel splice site mutation in MVK was found [47]. A possible causative link between MVK mutations and porokeratosis is that mevalonate kinase prevents UVA-induced apoptosis in keratinocytes [41].

Table 1 Clinical presentations associated with mutations in the MVK gene

Typical autoinflammatory diseases	Mevalonic aciduria Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS)
Inflammatory phenomena associated with MKD[a]	Ulcerative colitis Neonatal hepatitis
Diseases without systemic inflammation	Retinitis pigmentosa[b] Disseminated superficial actinic porokeratosis (DSAP) Porokeratosis of Mibelli

[a] Can be part of severe MKD phenotype and may be the initial presenting symptom in the absence of fever episodes

[b] Also, rare symptom of typical MKD

Conclusion

In the last 2 years, research on MKD has covered a range of subjects in pathogenesis and therapy. Also, the already broad spectrum of MKD phenotypes has been extended to include retinitis pigmentosa, colitis, and DSAP.

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